Outpatient Case

Ms. Medrano works as a hairdresser in Albuquerque. Seven months ago she began noticing stiffness in both hands in the morning that lasted longer and longer. Stiffness now lasts more than 1 hour every morning and includes her hands, wrists, and ankles. She has also has increasing difficulty standing for long periods of time at work or at home due to foot and ankle pain. She began taking ibuprofen 800mg 3 times a day and it had helped her to get through the day with less pain and stiffness.

Three months ago, Ms. Medrano noticed pain in her right and left shoulders when she would cut or blow dry her client's hair. She also began feeling extremely tired and short tempered. She had no energy to do her usual activities. Ibuprofen was no longer effective for her pain and stiffness.

One morning, Ms. Medrano could not lift her arms at all without extreme shoulder pain. She decided to make this appointment with you.

What symptoms are stand out or are concerning to you?

- Morning stiffness
- Joint pain in hands, wrists, feet, and ankles, shoulders
- Systemic symptoms (fatigue)

What follow up questions would you like to ask now that you have more history?

- Joint swelling
- Weight loss, fatigue, depressed mood, anorexia
- Review of systems to identify extra-articular manifestations (rash mucosal ulcers, chest pain, Raynaud phenomenon)
- Tobacco use
- Family history
- Ability to complete ADLs, iADLs

What would you focus on during the exam and what might you expect to find?

- tenderness and swelling of wrists, PIP, MCP joints (number and location of swollen or tender joints)
- positive squeeze test (grasp 2^{nd}-5^{th} metacarpals or metatarsals and squeeze laterally, note presence or absence of joint tenderness)
- boggy swelling (skin creases not visible)
- swan neck deformities in fingers
- normal muscle strength, but grip strength is reduced bilaterally
- skin rash

What is your differential diagnosis at this point?

- Viral polyarthritis (rubella, parvovirus, Hep B, Hep C, Chikungunya)
- Osteoarthritis
- RA
- Gout
- Fibromyalgia
- Sjogren's syndrome
- SLE
- Dermatomyositis
- Lyme disease
- Psoriatic arthritis

- Polymyalgia rheumatica

What are your top diagnoses? What makes them most likely?

How does fibromyalgia differ?

- typical symptoms: chronic, widespread MSK pain for > 3 months, absence of other systemic condition accounting for pain, excess tenderness in soft tissues, fatigue, sleep and mood disturbances, IBS
- exam: tender points- need 11 of 18
- treatment: sleep hygiene, CBT, exercise, acupuncture, yoga, amitriptyline, cyclobenzaprine, duloxetine, pregabalin

What history and exam findings would be more consistent with osteoarthritis?

- OA is DIP and CMC joints (RA is MCH and PIP joints)
- OA see Heberden's nodes (not in RA)
- OA, joints are hard and body (RA joints are soft, warm, and tender)
- OA, pain is worse after use, evening stiffness (RA worse after rest)
- OA, normal ESR, CRP, negative RF, anti-CCP

What presentation would be more consistent with gout?

- chronic inflammatory arthritis that results in monosodium urate crystal deposition in tissues or joints resulting from supersaturation of uric acid in extracellular fluids
- hyperuricemia
- acute episodic monoarthritis
- treatment of flare: colchicine, NSAIDs, glucocorticoids
- prevention: xanthine oxidase inhibition (allopurinol or febuxostat)

What lab work would you order?

- ESR, CRP, RF, anti-CCP antibodies, CBC (can show anemia), chemistry, LFTs, ANA , uric acid
- Consider TSH, CK
- Symptoms for less than 6 weeks: parvovirus, Hep B and C serology, Lyme titer
    - Also screen for Hep B and Hep C before initiating therapy
- PPD (before treatment)

WBC was 11. 4, Hgb and Hct were 12.9 and 44, platelets were 422. Chemistry and LFTs were normal.
TSH was normal.
ANA was also positive with a 1:40 titer and speckled pattern.
The blood tests showed a positive rheumatoid factor (1,060), CCP antibodies (131.4), elevated ESR (96) and CRP (4.7).
Hep B surface antigen was NR and Hep B surface antibody titer was < 3. Hep C antibody was nonreactive, quantiferon GOLD was nonreactive.

How do you interpret these results?

- RF positive in 70-80% of patients with RA (poor specificity, + in 5-10% of healthy individuals, 20-30% of patients with SLE, and other inflammatory conditions)
    - If > 3x upper limit of normal, more specific for RA
- Anti-CCP Ab, similar sensitivity, much higher specificity
- Low ANA titer, can be present in healthy individuals, but associated with a number of autoimmune diseases

    - In the homogeneous staining pattern, the entire nucleus is diffusely stained. Antibodies that produce this staining pattern include those directed against histone proteins, DNA, and DNA-histone complexes.
    - In the speckled staining pattern, fine or coarse speckles are seen throughout the nucleus. Many different antibodies may produce the speckled pattern, including those directed against U1 RNP, Sm, and La antigens.
    - The centromere pattern refers to the presence of 30 to 60 uniform speckles distributed throughout the nucleus of resting cells. In mitotic cells, the speckles localize to the chromosomes at the metaphase plate.
    - The nucleolar pattern refers to homogeneous or speckled staining of the nucleolus; it is produced by autoantibodies directed against fibrillarin, RNA polymerase I and III, Th, PM-Scl, and RNA helicase.
- ANA staining patterns are loosely associated with underlying autoimmune diseases. As an example, the most common ANA pattern in patients with mixed connective tissue disease is nuclear speckled, which is produced by antibodies directed against U1 RNP. In patients with limited systemic sclerosis, centromere staining is the predominant pattern; serum from patients with diffuse systemic sclerosis may produce speckled nuclear staining or nucleolar staining. Antibodies in the serum of Sjögren's syndrome patients are likely to produce speckled or homogenous staining. In patients with systemic lupus erythematosus (SLE), homogeneous, speckled, or nucleolar staining patterns may be observed.

What imaging studies would you order?
- x-rays of hands, feet, and shoulders (affected joints) – as baseline for monitoring
- consider CXR if pulmonary symptoms to evaluate for interstitial lung disease and pleural effusions

Consider arthrocentesis and synovial fluid analysis to exclude gout, pseudogout, or infectious arthritis

What about this patient's presentation is typical of the epidemiology and presentation of rheumatoid arthritis?
- women affected 2 to 4 times more often than men
- onset peaks between 40 to 60 years of age
- joint damage occurs most rapidly during the first several years of the disease
- genetic and environmental factors trigger autoimmune response
- joint swelling, pain, and stiffness of small peripheral joints (MCP, MTP, PIP, wrists)
- if treatment is not initiated within 4-6 months of diagnosis, RA can lead to progressive joint damage and increase the risk for later disability

What is the diagnostic criteria for rheumatoid arthritis?
Diagnosis:
- 2010 College of Rheumatology Classification Criteria for RA (>/= 6/10 is needed for classification of a patient as having definite RA):
    - Joint involvement:
        - 1 large joint – 0
        - 2-10 large joints – 1
        - 1-3 small joints – 2
        - 4-10 small joints – 3
        - > 10 joints – 5
    - Serology:
        - Negative RF and negative anti-CCP Ab – 0
        - Low-positive RF or low-positive anti-CCP Ab – 2
        - High positive RF or high-positive anti-CCP Ab – 3

- Acute phase reactants:
  - Normal CRP and normal ESR – 0
  - Abnormal CRP or abnormal ESR – 1
- Duration of symptoms:
  - < 6 weeks – 0
  - >/= 6 weeks – 1

What are the extra-articular manifestations of rheumatoid arthritis?

- Cardiac: accelerated atherosclerosis, pericarditis, myocarditis, CHF, atrial fibrillation
- Skin: rheumatoid nodules, vasculitis
- Eye: keratoconjuntivitis sicca, epicleritis, scleritis, peripheral ulcerative keratitis
- Hematologic: amyloidosis, Felty syndrome (splenomegaly, neutropenia, thrombocytopenia)
- Neurologic: cervical myelopathy, neuropathy
- Pulmonary: interstitial lung disease, pulmonary effusion, pulmonary nodules
- MSK: Osteopenia/osteoporosis, myositis
- Renal: glomerulonephritis

Ms. Medrano was referred to a rheumatologist, however, in the interim, you discussed with her that her diagnosis was rheumatoid arthritis and decided to begin treatment.

What treatment might you start?

- Low dose prednisone (5-10mg a day for 4-6 weeks)
- Steroid injections in joints (shoulders)
- DMARD (Disease Modifying Anti-Rheumatic Drug)-- Methotrexate and folic acid (7.5-15mg a week, single weekly dose)
  - Check for Hep B, Hep C and TB before initiating (if patient has latent TB, should complete at least 1 month of treatment before initiating biologic therapy for RA)
  - Increase dose as tolerated and as needed to control symptoms (increase by 2.5-5mg per week, no more frequently than every month)
  - Target is at least 15mg/week (maximum dose 25mg/week)

When is methotrexate contraindicated?

- frequent alcohol use or pre-existing liver disease
- women who are pregnant, contemplating pregnancy, or not using contraception
- severe renal impairment (GFR < 30)

What are other DMARDs?

- Nonbiologic:
  - Leflunomide
  - Hydroxychloroquine
    - Requires baseline eye exam
  - Sufalsalazine
- Biologic:
  - Adalimumab (Humira) - anti-TNF alpha
  - Etanercept (Enbrel) - anti-TNF alpha receptor
  - Infliximab (Remicade) – anti-TNF alpha

- Treating early (within 3 months of diagnosis) – twice as likely to achieve sustained remission
- Skin cancer screening if on biologic therapy
- Monitoring for infections
  - anti-TNF therapies—higher risk for developing opportunistic infections